ALASKA MEDICAID
PHARMACY AND THERAPEUTICS COMMITTEE

Location of Meeting
Frontier Building, 3601 C Street, Room 890/896

DRAFT MINUTES OF MEETING
November 20, 2009
8:00 a.m.

Committee Members Present:
Marvin Bergeson, MD
Amber L. Briggs, Pharm.D.
Richard E. Brodsky, MD
Robert H. Carlson, MD
Jeffrey G. Demain, MD
Vincent Greear, R.Ph.
Daniel P. Kiley, DDS, MPH
Diane Liljegren, MD (telephonic)
Paul Michaud, Pharm.D.
Claudia Phillips, MD
Jill Reid, R.Ph. (telephonic)
Janice L. Stables, MSN, ANP
White, Trish, R.Ph. (telephonic)

Committee Members Absent:
Dharna V. Begich, Pharm.D
Andrzej Maciejewski, MD
Sherrie D. Richey, MD

Others Present:
David Campana, R.Ph.
Melinda Sater, Pharm.D., First Health
Alex Malter, MD, MPH, Medicaid Medical Director
Chad Hope, Pharm.D.

1. Call to Order – Chair

The meeting was called to order at 8:00 a.m.

2. Roll Call

A quorum was present.

3. Public Comment – Local Public / Health Practitioners

DR. JENNY LOVE: Read a letter from the medical staff of the Alaska Psychiatric Institute. While the formulary will not affect the availability of medications for use within API, it will have an impact on the outcomes of our patients after discharge. Stabilization of a patient may require the use of a medication that is limited by Medicaid. This could result in a delay or difficulty in filling prescriptions in the outpatient setting, potentially resulting in patients going off their medications and placing them at risk. Limiting a patient's access to medication does not fiscally benefit the State of Alaska when it results in repeated admissions for inpatient psychiatric stabilization. We respectfully ask that the P&T Committee do not pursue any limiting of psychotropic medications. The risks to the patients do not outweigh the benefits to the state. Please keep access to psychotropic medications open and allow

practitioners to use their clinical and professional judgment to choose the right medications, not just those on a list, for their patients.

VERN STONER: Thanked the P&T Committee for providing one of the most flexible psychotropic prescribing arrangements in the United States, which should be maintained.

DAVID SAMSON: Alaska physicians currently have the ability to prescribe any psychotropic drug that they believe are necessary. Patients only improve when they stay on their medications. Studies indicate that patients stay on atypical medications much better than the old oral medications. Several different medications were discussed. The dissemination of Alaska's community mental health centers was described. We need to make it easy for prescribing physicians or nurse practitioners to continue with the medications that API prescribes at discharge without having to obtain prior approval.

DIXIE HOOD: A licensed marriage and family therapist from Juneau said many of her clients stopped using their medications due to side effects or other issues. There needs to be a wide variety of prescription options for antipsychotics, antidepressants and other medications so patients have the best treatments available. The patients' options should not be reduced in a desire to save costs.

BETH LACROSSE: I am speaking today not only as the president of NAMI Ketchikan, but also as a person who lives with mental illness every day. Mental illnesses, just like medical illnesses, can be controlled through medication. My personal experience with antipsychotic drugs started in 1983. During that time, I was able to try many different antipsychotic drugs until we found the one that worked. I am advocating for open access to antipsychotic medications for the treatment of mental disease. I am living proof that medication works. It is important to be able to find the right drug for the right person, often through a trial by error process. Everyone that lives with mental illness has a right to quality of life and therefore there should be unrestricted access to all antipsychotic medications.

JEANETTE GRASCO: A past president of NAMI Alaska read a letter regarding medications used to treat mental illness. NAMI Alaska and its affiliates throughout the state provide support, education, and advocacy for people dealing with mental health issues, their families, friends, and the community. NAMI Alaska is concerned about the potential of restricting access to particular medications. NAMI Alaska's policies and recommendations were reviewed. Unrestricted access to antipsychotics is the most desirable for the clinical wellbeing of people with mental illness. We reject step-therapy and prior authorization policies that require trying older medications before newer medications can be tried. We also oppose switching consumers who are stable on a current antipsychotic, because it threatens continuity of care and results in a high cost and poor outcome. It is not cost effective for people to remain untreated because they cannot access the medications that can help them. There is also a tremendous cost to both the families and the communities if patients remain untreated. We advocate for open formulary access to all mental health medications, including atypical antipsychotics, second-generation anticonvulsants, ADHD medications, SSRIs and SNRIs. This open formulary will provide patients and providers with access to the most appropriate therapeutic options in treating mental illness, which will guarantee better clinical and cost effective outcomes. We remain opposed to state policy changes that put cost ahead of consumer care.

TOM OBERMEYER: I work for Senator Davis, the chair of the Senate Health Committee, but I am here as an individual. It is marvelous that you allow such a broad spectrum of drugs to be available. A recent New York Times article indicated that Congress is looking into the fact that the pharmaceutical

companies have increased their costs by 35 percent since 2006, and 9 percent since last year. I understand that there is an arrangement to provide a discount of 15 to 17 percent for drugs on the formulary, but I wonder if the state is really getting that benefit considering the overall increase in the cost of the drugs. With the ongoing review, Congress is considering the possibility that the increase is due to the anticipated provisions in the Healthcare Reform Act. Every patient in this state should get the drugs that they need, but we also need to ensure that the state gets the benefit of the appropriate discounts.

JERRY JENKINS: Anchorage Community Health Services currently has five providers. Their position is that an open formulary is better for consumers, because it allows more choices and treatment strategies. It also allows prescribers individualized and targeted care for unique situations. If restrictions have to occur, we believe that the following would be more cost effective. Preauthorization when multiple psychotropic medications of the same classification are used concurrently, particularly those of an atypical antipsychotic type, and restricting off label use of psychotropics for children.

4. Re-Review of Atypical Antipsychotics (Red Category)

ELHAM TABARSI: A representative of Astra Zeneca discussed Seroquel and Seroquel XR, which are the only atypical antipsychotic agents with proven efficacy in bipolar depression. Seroquel XR is the only oral atypical antipsychotic agent for acute depressive, manic and mixed episodes of bipolar disorder at monotherapy. The dosages, indications, and adverse reactions were reviewed.

DAVID SAMSON: Reviewed the generic drugs available. Some of the cost considerations will be answered by more drugs becoming available in generic formulations. To ensure that our patients who use atypical antipsychotics remain safe, we should not change our current method of doing business.

DAVID GROSS: A representative of Pfizer discussed Geodon (Ziprasidone). Geodon provides proven efficacy in treating both positive and negative symptoms of schizophrenia, acute exacerbation of symptoms in both schizophrenia and schizoid-effective disorder, and the prevention of a relapse with long-term use. It is also indicated for patients with acute manic or mixed episodes, with or without psychotic features associated with bipolar disorder. It has a well-established safety and favorable tolerability profile with neutral effects, and in some cases improvement, relative to other atypical antipsychotics, on weight gain and metabolic parameters. Geodon has both oral and intramuscular formulations. Common to both schizophrenia and bipolar disorder is a significant rate of comorbid medical conditions such as cardiovascular disease, obesity, and diabetes, translating into significant elevations in mortality and reductions in lifespan. Several trials and their outcomes were discussed. Geodon has several therapeutic benefits and proven advantages over other agents in this class. It provides powerful efficacy without compromising overall patient health. It is well recognized by researchers and physicians in the field that there exists many differences among atypical antipsychotics. We believe it is important to have open access so clinicians can provide the best care for their patients and match the appropriate medicine to an individual patient.

KIM PORTLAND: A representative of Merck discussed Saphris (asenapine), the first atypical antipsychotic to gain simultaneous indicates for the treatment of acute schizophrenia in adults, and acute manic or mixed episodes associated with bipolar I disorder, with or without psychotic features, in adults. It is also the first atypical antipsychotic to launch with a sublingual formulation. It is placed under the tongue, dissolves in seconds, and leads to a peak plasma concentration within .5 to 1.5 hours.

This may lead to greater compliance, because cheeking of this medication is virtually impossible. Efficacy data, dosing, and clinical trials were reviewed. Efficacy is important, but safety and tolerability profiles allow us to see how well patients can stay on these medications for the long-term. Saphris has the same class warnings as the other atypical antipsychotics. The common adverse effects were reviewed.

KIM LODMEYER: A representative of Bristol-Myers Squibb discussed Abilify (Aripiprazole). There are currently 13 FDA-approved indications for once-daily dosing of Abilify, which were summarized. The newest data is focused in pediatrics and major depressive disorder. Several trials and their outcomes were reviewed. An SNVA has been filed for the treatment of irritability associated with autistic disorder in pediatric patients 6 to 17 years old, which is currently under FDA review. A claims data analysis was conducted to compare time to psychiatric rehospitalization in patients with bipolar disorder who were treated with a mood stabilizer plus an atypical. Adjunct of Abilify was associated with a longer time to rehospitalization and significantly lower psychiatric costs than all other atypicals during a 90-day follow up period. The box warnings were reviewed. Abilify has the broadest range of indications across adult and pediatric populations and is only one of two atypicals with FDA approval in youth less than 19 years of age. As such, Abilify should remain available as a first line agent and open access to atypicals should be preserved in the State of Alaska.

STEVEN CHANG: A representative of Eli Lilly discussed Zyprexa, which has a new FDA indication as of March 2009 for Zyprexa and Fluoxetine in combination for the acute treatment of depression in adults. Two new meta-analysis studies on antipsychotics in the treatment of persons with schizophrenia and their outcomes were reviewed. We request that Zyprexa be included on the PDL.

Dr. Sater gave the First Health presentation on Atypical Antipsychotics. There are eight available chemical entities in this class, 10 available products, and one combination with Fluoxetine. All single entity products are indicated for the treatment of schizophrenia. Other indications vary by product. Developed in response to problems with atypical antipsychotics, including lack of efficacy, lack of improvement in negative symptoms, and troublesome adverse drug reactions, we now have these atypical agents. These agents are serotonin dopamine antagonists, although specific receptor binding and affinity varies widely. All agents carry box warnings regarding the use in elderly patients with dementia-related psychosis, and there are other box warnings that vary by the agent. Clozapine carries the most warnings and contraindications of any drug in this class. All drugs carry warnings about hyperglycemia, sometimes extreme and associated with DKA, hyperasmolarcoma, or death. The newer agents, Geodon, Invega and Abilify, do not demonstrate the wealth of evidence for hyperglycemic and metabolic issues as the older agents. In October, there were 4,514 claims. By comparison, there were 307 claims for typical antipsychotics. There were 13 claims for Symbyax. Of the atypical antipsychotics, 1,480, or 33 percent, were prescribed for patients under the age of 18. The currently preferred agents are Seroquel, Abilify, Risperidone, Zyprexa, Geodon, and Clozapine. In October, the breakdown of the claims were: 25% for Seroquel, 23% for Abilify tablets, 18% for Risperidone tablets, 14% for Zyprexa, 7% for Geodon, 3% for Clozapine, 2.2% for Seroquel XR, and less than 6% for the remaining agents. At the last review, there was significant discussion of class effect and how best to address this challenging class. It concluded with the adoption of the phrase therapeutic alternative. A motion stating that all drugs were a therapeutic alternative and at least one product from each chemical entity be added to the PDL, passed unanimously. Since the last review, Saphris has been added to the marketplace. Dr. Von Hafften still believes that one product from each chemical entity should be available on the PDL.

In response to Dr. Phillips, Dr. Sater said there was no information available that Saphris is more effective or easier on the system than the other agents.

DR. KILEY MOVED THAT THE DRUGS IN THIS CLASS WERE THERAPEUTIC ALTERNATIVES AND NO PREFERENCE IS EXPRESSED. SECONDED BY DR. BERGESON.

Dr. Liljegren expressed concerns about the motion. People respond to these medications differently and the consequences of ineffective treatment are great. Psychiatrists need to be provided with a full range of atypical antipsychotics. At least one medication from each class should be included on the PDL. In response to Dr. Brodsky's notation that if the motion were amended then Saphris would also be included on the PDL, Dr. Liljegren said she would be willing to support a motion that included one medication from each class, excluding Saphris.

Dr. Sater defined the term therapeutic alternatives, which took the place of the older term of class effect. Therapeutic alternative means that you acknowledge that there are differences between agents, but you agree that these agents represent treatment alternatives for the conditions in question. Dr. Von Hafften still recommends including one product from each chemical entity, but he was not directly asked about Saphris.

In response to Dr. Demain, Dr. Sater said there were no specific concerns about Saphris. The most concerning drug in this class, which is also the most effective, is Clozapine.

THE MOTION FAILED WITH SEVEN OPPOSED.

DR. DEMAIN MOVED THAT THE DRUGS IN THE CLASS WERE THERAPEUTIC ALTERNATIVES, AND ONE ENTITY FROM EACH CLASS SHOULD BE INCLUDED ON THE PDL. SECONDED BY DR. LILJEGREN.

In response to Dr. Bergeson, Mr. Campana said the committee should deal with the motion and then provide direction to the DUR Committee to look at the indications, side effects and utilization figures.

Dr. Bergeson discussed the side effects on children. He felt that atypical antipsychotics should not be limited and the decision should be left up to the psychiatrists. As the number of psychiatrists in Alaska continues to decline, primary care physicians are prescribing more of these drugs.

THE MOTION PASSED WITH ONE OPPOSED.

5. Re-Review of Anti-Depressants Other (Red Category)

There were no public testimonies.

Dr. Sater gave the First Health presentation on Anti-Depressants Other. There are four available entities in this class, many different products, many different salts, both extended release and immediate release. The mechanisms of action differ between the agents. The adverse drug reactions vary between agents, as do the indications and therapeutic uses. In October, there were 1,517 claims:

44% for Trazodone, 11.5% for Mirtazapine, 10% for sustained release Bupropion, 9% for Bupropion XL 300, 8% for Bupropion XL 150, 6% for Wellbutrin XL 150, 6% for Wellbutrin XL 300, 4% for plain Bupropion, and less than 1% for the remaining agents. At the last review, this class was considered separately from the SNRIs. After a brief discussion, a motion stating all drugs were therapeutic alternatives and at least one of each chemical entity, including at least one once-daily formulation, be included on the PDL, passed with one opposed. Since the last review, Aplenzin, a new salt of Bupropion HBr, has been added to the marketplace. Dr. Van Hafften feels that one agent from each chemical entity, with sustained release products where available, is appropriate for this class.

DR. PHILLIPS MOVED THAT THE DRUGS IN THIS CLASS WERE THERAPEUTIC ALTERNATIVES AND AT LEAST ONE CHEMICAL ENTITY, INCLUDING AT LEAST ONE ONCE-DAILY FORMULATION, BE INCLUDED ON THE PDL. SECONDED BY MS. STABLES. THE MOTION PASSED UNANIMOUSLY.

6. Re-review of Anticonvulsants 2nd Generation (Red Category)

DORNA CHU: A representative of UCB discussed Vimpat (Lacosamide). Vimpat tablets are indicated as an add-on therapy in the treatment of partial onset seizures in patients with epilepsy, age 17 years and older, and Vimpat injection for IV uses when oral administration is temporarily unfeasible. Vimpat has the first novel mechanism of action introduced into this class in almost 10 years, which was described. The dosages were reviewed. The efficacy and safety of Vimpat for the treatment of partial onset seizure has been studied extensively in over 1,300 patients in three trials, which were reviewed. It is generally well tolerated with no clinically relevant effects on vital signs, lab parameters, or body weight. The adverse events, which are generally mild to moderate, were reviewed. In the clinical trials, discontinuation rates due to adverse events were low. No plasma level or lab monitoring is required. Cardiac and respiratory monitoring is not required when using the IV formulation. Based on efficacy and tolerability profiles, we request that you add Vimpat to the PDL.

JENNIFER BRZANA: A representative of GlaxoSmithKline, discussed Lamictal XR (Lamotrigine) and the orally dissolving tablet, or ODT. In May, both the XR and ODT formulations of Lamotrigine received FDA approval. We do not anticipate either formulation will have a huge financial impact to your system, as neither product is intended to replace immediate release Lamotrigine. Both are designed for specific populations that may benefit from altered delivery systems. Lamictal XR is indicated as adjunctive therapy for partial onset seizures, with or without secondary generalization, in patients 13 years of age or older. It is not indicated for the treatment of bipolar I disorder. It has the proven efficacy and tolerability of Lamictal, with the convenience of once-daily dosing. The safety and efficacy was well established in two clinical trials, which were reviewed. It carries a boxed warning concerning serious rashes, which is not expected to differ from that of immediate release Lamotrigine. Lamictal ODT shares the same indications as immediate release Lamictal in both epilepsy and bipolar I disorder. It is bioequalvent to immediate release Lamotrigine, but it is not therapeutically equivalent. It was brought to the market to offer benefits to patients with epilepsy or bipolar disorder that have trouble swallowing. In a survey of 947 patients in a general practice setting, 23 percent reported difficulty swallowing pills, and 14 percent delayed taking their therapy, 8 percent skipped doses, and 4 percent discontinued therapy altogether due to this swallowing difficulty. Lamictal XR and Lamictal ODT should be available on the PDL.

DAVID GROSS: A representative of Pfizer discussed Lyrica (Pregabalin). Lyrica is in this class of drugs, but it has a very broad list of indications including adjunctive use in the treatment of adults with partial onset seizures. It also has several other indications, which were reviewed. Lyrica has proven to be safe and efficacious as demonstrated in several trials, which were discussed. Last year you saw the value of Lyrica in treating patients with seizures, neuropathic pain, and fibromyalgia. I hope you continue to see Lyrica's value and make it available on the PDL.

Dr. Sater gave the First Health presentation on Anticonvulsants, Oral. There are a number of available entities and many different dosage forms, branded and generic products, in the second-generation anticonvulsants. The mechanisms are not clearly understood for some of the drugs and vary widely between the agents. Adverse drug reactions and efficacy also vary widely, as do therapeutic uses between the agents in this class. The currently preferred agents are Gabapentin, Lamotrigine, Topiramate, Lyrica, Levetiracetam, Zonisamide, Gabitril, Lamictal tablets, Lamotrigine tablets, Neurontin solution, Neurontin, Zonegran, Lamictal ODT, Topomax sprinkle tabs, and Lamictal DS. In October, there were 2,288 claims: 30% for Gabapentin, 21% for Lamotrigine, 17% for Topiramate, 10% for Lyrica, 6.5% for Levetiracetam tablets, 3% for Topomax tablets, and less than 10% for all the rest of the products. At the last review and without discussion, a motion stating all drugs were therapeutic alternatives and at least one agent from each chemical entity be included on the PDL failed. A brief discussion of the use of the medically necessary clause, a motion suggesting all agents are therapeutic alternatives and to accept the bids received from the process, passed with four opposed. Since the last review, Vimpat, Lamictal XR, and Lamictal ODT were added to the marketplace.

In response to Dr. Demain, Dr. Sater said they did not know what percentage of the prescriptions was for seizure disorder versus other conditions, but it probably varies widely by individual agent.

DR. KILEY MOVED THAT THE DRUGS IN THIS CLASS WERE THERAPEUTIC ALTERNATIVES AND NO PREFERENCE BE EXPRESSED. SECONDED BY MR. GREEAR.

Dr. Liljegren expressed concern about not having at least one drug from each class. The medications vary widely and some have multiple indications. The motion could result in excluding some very important medications, as well as drugs for certain indications like migraines and fibromyalgia. Dr. Bergeson noted that there were numerous generic drugs available in this class, which would cover most of the chemical entities. The medically necessary clause could always be utilized.

THE MOTION PASSED WITH THREE OPPOSED.

7. Re-review of ADD/ADHD and Related Agents (Red Category)

ANGELA LEDAY: A representative of Shire discussed Vyvanse and Intuniv. Vyvanse is the first pro-drug stimulant for the treatment of ADHD. It is indicated for children ages 6 to 12, as well as adults. Several trials and studies were reviewed. Due to its formulation as a pro-drug, it does not rely on GI factors for its relief. With over 5.2 million prescriptions being dispensed for Vyvanse, the daily average consumption is 1.0, which is consistent with the once-daily recommended dose. It is the only stimulant medication with clinically demonstrated data to show efficacy in treating the core symptoms of ADHD for up to 13 hours. It has an extended duration of action in the adult population as well. It provides a consistent delivery and is not affected by changes within the GI tract. Ivtuniv is a selective

alpha-2A adrenergic agonist, which is approved for the treatment of ADHD in children and adolescents 6 to 17 years old. It is a once-daily extended release formulation and is available as 1, 2, 3 and 4-milligram tablets. This is a non-stimulant therapy so it can be used in patients who have not achieved adequate responses to stimulants or by parent and physicians who prefer to use a non-scheduled option as a first line treatment for ADHD. Its efficacy has been demonstrated in both children and adolescents 6 to 17 years old with minor side effects that are mild to moderate in intensity.

STEVEN CHANG: A representative of Eli Lilly discussed Strattera. It was the first non-controlled ADHD agent indicated for children, adolescents and adults. It is the first medication FDA indicated for the maintenance treatment of ADHD in children and adolescents. The safety and efficacy of Strattera in the maintenance of ADHD was demonstrated in an 18-month trial, which was reviewed. Strattera may also be considered as the first medication for ADHD in persons with an active substance abuse problem, comorbid anxiety or ticks. It is preferred if a patient experiences severe side effects to stimulants. Availability of Strattera may help address current, unmet medical needs in the treatment of ADHD. Safety information, including box warning for suicidality, is contained on the package insert, which can be provided upon request.

ROBERT HOST: A representative of Cepalon discussed Nuvigil. It does not have an indication for ADD or ADHD, but like Provigil, it is often included in this class for review. Nuvigil is indicated to improve wakefulness in patients with excessive sleepiness associated with obstructive sleep apnea, shift work sleep disorder, and narcolepsy. The pharmacokinetic differences between Nuvigil and Provigil were reviewed. Several trials and their outcomes were reviewed. The warnings of adverse events are similar to Provigil. Nuvigil provides wakefulness throughout the day and the overall clinical condition in patients with ES associated with obstructive sleep apnea, shift work sleep disorder, and narcolepsy.

Dr. Sater gave the First Health presentation on ADD/ADHD and Related Agents. There are nine available entities in this class with many different products, both immediate and extended release. There is also one transdermal preparation. Modafinal and Armodafinal do not have a pediatric indication at this time. Atomoxetine has a unique mechanism of action. The agents in this class are used in both adults and children with approximately 9 percent of the claims being for adult patients. There is similar efficacy between all agents, but much variability in patient response. The currently preferred agents are Concerta, Strattera, Focalin XR, Methylin, Amphetamine salt combinations, Adderall XR, Provigil, Methylphenidate, Dextroamphetamine, generic Dexmethylphenidate, Methylin ER, all the Methylin products, and generic Methylphenidate. In October, there were 2,003 claims: 27% for Concerta, 14% for Strattera, 11% for Focalin XR, 11% for Dextroamphetamine capsules 24 hours, 6.5% for Methylin tablets, 6.5% for Amphetamine salt combinations, 4.5% for Adderall XR, and less than 15% for all the rest of the agents combined. At the last review, there was very little discussion. A motion to prefer a short-acting and a long-acting Methylphenidate product, including but not limited to Concerta, a short-acting and a long-acting Dextroamphetamine product, Strattera and Provigil passed with seven opposed. Since the last review, Liquid was removed from the marketplace and was replaced by Procentra, but they are exactly the same product. Nuvigil was added to the marketplace. Some limited stimulant induced weight loss trials in adults were published.

Dr. Bergeson noted that since the last review, Adderall has gone generic and Concerta is due to go generic.

DR. KILEY MOVED THAT THE DRUGS IN THIS CLASS WERE THERAPEUTIC ALTERNATIVES AND AT LEAST ONE EXTENDED RELEASE AND ONE NON-STIMULANT ENTITY SHOULD BE INCLUDED ON THE PDL. SECONDED BY DR. BERGESON. THE MOTION PASSED UNANIMOUSLY.

8. Re-review of Antidepressants SNRI (Red Category)

STEVEN CHANG: A representative of Eli Lilly discussed Cymbalta. It is currently approved by the FDA for four indications for adults, which include major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathic pain, and fibromyalgia. Recently presented health economic data relating to Cymbalta for diabetic peripheral neuropathic pain and fibromyalgia was reviewed. Several trials and their outcomes were reviewed. Cymbalta is not approved for use in patients under the age of 18. Full prescribing data can be provided upon request.

LISA MCKENZA: A representative of Pfizer discussed Pristiq. Major depressive disorder is a debilitating illness that is associated with a high, unmet medical need. Options are important, particularly for those patients who do not respond to currently available therapy or have residual symptoms. Pristiq is the first antidepressant approved by the FDA in the past five years. The efficacy and safety of Pristiq was established in four trials in adults with major depressive disorder over a treatment period of 8 weeks. The recommended dose is 50 milligrams, once a day, without regard to meals and no titration is necessary. The safety profile and adverse reactions were reviewed. The prescribing information for all antidepressants, including Pristiq, has a black box warning that describes a risk of suicidality in children and adolescents taking antidepressants. Pristiq is not approved for the treatment of children and adolescents. Pristiq's pharmacokinetic profile differs from other members of the SNRI class, which was reviewed.

JAKE KNEE: A representative of Forest discussed Savella, which has a single indication for fibromyalgia. It is the newest of the three fibromyalgia agents currently approved in the United States. Savella's unique properties were explained. Several clinical trials and their outcomes were reviewed. Since Savella has been available in Europe for 10 years with over a billion doses prescribed, there is a large safety database available. This is the only fibromyalgia medication that has statistical significance in the domain of fatigue. It is also weight neutral, with small weight loss in the clinical trials. When you look at the cost and daily consumption of Savella, you will be impressed with the savings over the other medications available. Savella should be included on the PDL due to its unique mechanism of action, stringent clinical profiles and cost advantages.

DR. (INDISCERNIBLE): A representative of Upstate Pharma discussed Venlafaxine ER tablets, which were approved in July 2008 for the treatment of major depressive disorder and social anxiety disorder. It is not indicated for panic disorder or generalized anxiety disorder. Several studies and their outcomes were reviewed. Venlafaxine ER is considered by the FDA to be a pharmaceutical alternative to Effexor XR capsules. Both formulations should be titrated and taken with food; however, the capsule may be opened and sprinkled on food while the tablets must be swallowed whole. Similar efficacy and side effects can be expected from both Venlafaxine ER tablets and Effexor XR. We request that Venlafaxine ER tablets be included on the PDL.

Dr. Sater gave the First Health presentation on Antidepressants SNRI. There are four available entities in this class with many different products, both extended and immediate release. The mechanisms of action differ between the agents. The adverse drug reaction profiles are dissimilar. Indications and therapeutic uses also differ between agents. The currently preferred agents are Cymbalta, Effexor XR, and generic Venlafaxine immediate release. In October, there were 1,115 claims: 52% for Cymbalta, 36% for Effexor XR, 7.5% for Pristiq, and less than 10% for all the rest. At the last review, the class was considered separately from the other antidepressants, as it is this year. After a very brief discussion, a motion for a class effect, including at least Duloxetine and Venlafaxine, including once-daily preparations where available, passed unanimously. Since the last view, Savella has been added to the marketplace and is only indicated for the treatment of fibromyalgia.

MS. STABLES MOVED THAT THE DRUGS IN THIS CLASS, EXCEPT FOR SAVELLA, WERE THERAPEUTIC ALTERNATIVES, AND AT LEAST ONE OF THE FIBROMYALGIA INDICATED MEDICATION SHOULD ALSO BE INCLUDED ON THE PDL. SECONDED BY DR. BERGESON. THE MOTION PASSED UNANIMOUSLY.

Dr. Sater noted that she would no longer be the P&T Committee's regularly assigned clinical manager, but would remain with them until her replacement was assigned.

Break from 9:56 a.m. to 10:15 a.m.

9. Review of Skeletal Muscle Relaxants (Red Category)

ROBERT HOST: A representative of Cephalon discussed Amrix. It is an extended release formulation of Cyclobenzaprine. It is the first and only once-daily skeletal muscle relaxant. Amrix is specifically formulated to allow for the early systemic exposure of Cyclobenzaprine's sustained release of the active drug, reducing fluxuations in plasma levels. Several studies and their outcomes were reviewed. In the safety profile, Amrix was well tolerated and the majority of adverse events were mild in severity. The dosage, which is once daily, was reviewed. Amrix should only be used for short periods, up to two to three weeks. We request that Amrix be included on the PDL.

Dr. Sater gave the First Health presentation on Skeletal Muscle Relaxants. There are nine chemical entities in this class with many available branded and generic products. Three are available as combinations with aspirin. Cyclobenzaprine is available as immediate and extended release products. The agents in this class either are approved for adjunct treatment of acute, painful muscular skeletal conditions or for spasticity associated motor neuron. Mechanisms of action, adverse drug reaction profiles and efficacy vary widely among the agents. Many of the agents are centrally active. In October, there were 1,368 claims: 46.4% for immediate release Cyclobenzaprine, 19% for Baclofen, 16% for Tizanidine, 6.5% for Carisoprodol, 4.3% for branded Zanaflex, 3.3% for Carisoprodol, 3.2% for Skelaxin, 1% for Amrix, and less than 1% for the rest. This is a new class and no one wanted to discuss this class.

Dr. Liljegren felt Carisoprodol (Soma) should not be included on the PDL, because it is an inferior drug and habit forming. Mr. Campana said the DEA would be placing Soma on Schedule 4. We currently require prior authorization for Soma with a 14-day limited supply. The prescription cannot be continued and requires a new prior authorization every two weeks.

Dr. Liljegren also felt that at least one other drug besides Cyclobenzaprine should be included on the PDL due to drug interactions. Mr. Campana noted that there were many generics available in this class and another alternative to Cyclobenzaprine would likely be available if a class effect were declared.

DR. LILJEGREN MOVED THE DRUGS IN THIS CLASS WERE THERAPEUTICALLY EQUIVALENT, WITH SOMA BEING EXCLUDED, AND AT LEAST ONE OTHER MEDICATION BESIDES CYCLOBENZAPRINE BEING INCLUDED ON THE PDL. SECONDED BY DR. DEMAIN.

Dr. Demain clarified that the motion would not necessarily prefer Cyclobenzaprine.

Dr. Briggs did not feel it was necessary to exclude Soma, because there were already limitations on it. Dr. Liljegren felt the committee's job was to exclude the drug due to its inferiority, regardless of whether another committee had already placed restrictions on its use. In response to Dr. Demain, Mr. Campana said the motion would classify Soma as a non-preferred drug and the current edits would continue.

THE MOTION FAILED WITH SEVEN OPPOSED.

DR. CARLSON MOVED A CLASS EFFECT. SECONDED BY DR. BRIGGS. THE MOTION PASSED WITH THREE OPPOSED.

10. Re-Review of Opioids – Long Acting (Red Category)

There were no public testimonies.

Dr. Sater gave the First Health presentation of Opioids – Long Acting. There are five available entities in this class. There are four oral morphine dosage forms: oral Oxycodone, Oxymorphone, Methadone, and Transdermal Fentanyl. Morphine is also available in combination with Naltrexone, which is a new entry in this class. All are new receptor antagonists with the same mechanism of actions, similar efficacy and side effect profiles. The pharmacokinetic parameters are quite different. Many products carry black box warnings regarding extreme potency, abuse potential, and potential overdose of patients. The currently preferred agents are Methadone, sustained release Morphine, Kadian, Opana ER, Duragesic, Methadone solution, and sustained release Oromorph. In October, there were 740 claims: 29% for OxyContin, 23% for Methadone, 21% for sustained release Morphone, 12% for Fentanyl patches, 7.5% for Kadian, 2.3% for Avinza, 2% for Opana ER, 1.5% for Duragesic patches, and less than 2% for all the rest. Last year, this was a blue class. Without discussion, the motion to include one transdermal and one oral preparation, one long-acting Morphine product, and Methadone, passed unanimously. Since the last review, Embeda, Morphine sulfate and Naltrexone hydrochloride, was added to the marketplace.

In response to Dr. Carlson, Dr. Sater said that if a class effect were declared, the drugs on the PDL would probably be similar to the current PDL. There may be a few minor changes, but Methadone probably would not be a preferred agent. Dr. Malter noted that Methadone was available generically.

DR. CARLSON MOVED A CLASS EFFECT TO INCLUDE METHADONE AND ONE TRANSDERMAL PREPARATION ON THE PDL. SECONDED BY DR. BRIGGS.

The committee reviewed the proposed motion to last year's motion and reviewed the drugs that were available as generics.

THE MOTION PASSED UNANIMOUSLY.

11. Re-review of Opioids – Short Acting (Red Category)

There were no public testimonies.

Dr. Sater gave the First Health presentation on Opioids – Short Acting. There are two available dosage forms, but we are only considering Fentanyl in this group. All agents in this class currently require a prior authorization. They are only for use in Opioid tolerant patients. Their sole FDA approved indication is for the management of breakthrough cancer pain in patients already receiving Opioids. In October, there were 2 claims: 1 for Actiq and 1 for Fentora. This was a green class last year. Without discussion, a motion for class effect passed unanimously. Since the last review, Onsolis was added to the marketplace.

DR. LILJEGREN MOVED THAT NONE OF THE DRUGS IN THIS CLASS BE PREFERRED. SECONDED BY MR. GREEAR.

In response to Dr. Demain, Dr. Sater said Miparadine had not been withdrawn. For the purposes of grouping classes, this portion was carved out due to the rebates available. If a class effect is declared, Miparadine will not appear on the PDL.

Mr. Campana said that although there were not many prescriptions for this class, the cost of these drugs is very high.

The committee discussed what the advantage was to not preferring any of the drugs in this class. Dr. Liljegren felt it was not necessary to prefer any of the agents, because there was almost ways an alternative drug that could be used. Dr. Demain noted that there were people who were allergic to Opioids, but could tolerate Fentanyl. Dr. Briggs noted that there was a role for the drugs in this class, although it was limited. Mr. Campana pointed out that these drugs required a prior authorization, unless it was for a cancer patient.

THE MOTION FAILED WITH ELEVEN OPPOSED.

DR. DEMAIN MOVED A CLASS EFFECT. SECONDED BY DR. BRIGGS. THE MOTION PASSED WITH ONE OPPOSED.

12. Review of Progestins (Red Category)

There were no public testimonies.

Dr. Sater gave the First Health presentation on Progestins. There is only one available chemical entity in this class, with two products. Both products are indicated for cachexia associated with AIDS. However, both are used to treat cachexia resulting from other conditions. The products produce

equivalent serum concentrations and have equivalent efficacy. In October, there were 7 claims: 57% for Megestrol Acetate and the remainder for Megace ES. This is a new class that has not been discussed. No physicians wanted to comment on this class.

MR. GREEAR MOVED A CLASS EFFECT. SECONDED BY DR. DEMAIN. THE MOTION PASSED UNANIMOUSLY.

13. Re-review of Proton Pump Inhibitors (Red Category)

GUSTAVAS ARANDA: A representative of Takeda Pharma discussed Kapidex. It is the only FDA approved dual delayed release proton pump inhibitor indicated for the healing of all grades of erosive esophagitis, the maintenance of severe erosive esophagitis, and treating heartburn associated with non-erosive GERD. The dosage forms and strengths were reviewed. Kapidex is the only PPI to incorporate a dual delayed release formulation that results in a plasma concentration timed profile with two distinct peaks. The first peak occurs 1 to 2 hours after administration, followed by a second peak 4 to 5 hours after administration. Kapidex was well tolerated in clinical trials involving over 6,000 patients with adverse events similar to that of placebo and Lansoprazole. The most frequent adverse events were reviewed. We request that Kapidex be included on the PDL.

DOUG SCARSDALE: A representative of Astra-Zeneca discussed Nexium. Nexium differs from Omeprazole in its metabolism in that it has less variability based on the CYP450 system. In head-to-head trials, it demonstrated significantly greater acid control compared to the other PPIs. It was found to have consistently high healing rates across all grades of erosive esophagitis. Nexium is approved for use in pediatrics and adolescent patients, 1 to 17 years of age, for the short-term treatment of GERD. The most common adverse events were reviewed. There are no new safety concerns identified in pediatric patients. Nexium capsules can be opened and sprinkled on applesauce or suspended in water, as well as administered through nasal gastric tubes or IVs. Nexium should be included on the PDL.

Dr. Sater gave the First Health presentation on Proton Pump Inhibitors. There are six available entities and seven branded products. FDA approved indications vary, but all drugs are used for all indications in clinical practice. Adverse drug reaction profiles and efficacy are similar across the class. The currently preferred agents are Nexium and Prevacid. In October, there 2,151 claims: 35% for Nexium, 22.5% for Omeprazole, 22.5% for Prevacid, 11.5% for Pantoprazole, 5% for Prevacid rapid dissolving tabs, and less than 5% for all the rest. At the last review, a motion for class effect, including preparations suitable for pediatric patients and people on tube feedings or the equivalent, passed unanimously. Since the last review, Kapidex was added to the marketplace. We received many letters from the community supporting Kapidex, because they feel the drug is more potent, works better, and is better tolerated. Dr. Richard Farley indicated that he supports the use of either Pantoprazole or Rabeprazole secondary to the decreased interaction with Clopedigrol (ph).

Dr. Campana explained why some of these drugs required prior authorization. The drugs are often used indefinitely and at high doses, even though it may or may not be warranted. When the prior authorization first went into effect, we had quite a decrease in utilization.

Dr. Sater gave an overview of the decreased utilization in this class. In December 2003, there were over 5,200 claims for drugs in this class. The Medicaid Part D people were removed. We saw a decrease of a quarter to a third when the prior authorization went into effect.

Dr. Brodsky felt that far too many people were prescribed PPIs and for too long of a period.

DR. DEMAIN MOVED A CLASS EFFECT TO INCLUDE ONE PEDIATRIC APPROPRIATE AGENT. SECONDED BY DR. CARLSON. THE MOTION PASSED UNANIMOUSLY.

14. Re-review of Sedative/Hypnotics (Red Category)

There were no public testimonies.

Dr. Sater gave the First Health presentation on Sedative/Hypnotics. There are 10 available entities, both immediate release and extended release, in this class. There are two classifications: Benzodiazepines, both short and long acting, and non-Benzodiazepines. Rozerem has a unique mechanism of action. In October, there were 1,141 claims: 36% for immediate release Zolpidem, 23.4% for Ambien CR, 16.7% for Temazepam, 10.5% for Lunesta, 8% for Rozerem, 2.5% for Triazolam, 1.3% for Ambien, and less than 3% for all the rest. This was a blue class last year. Without discussion, the motion to include at least one Benzodiazepine, at least one non-Benzodiazepine, Rozerem and a short-acting Zolpidem product passed unanimously. Since the last review, Edluar has been added to the marketplace.

DR. LILJEGREN MOVED TO INCLUDE AT LEAST ONE BENZODIAZEPINE, AT LEAST ONE NON-BENZODIAZEPINE, ROZEREM, AND A SHORT-ACTING ZOLPIDEM ON THE PDL.

THE MOTION FAILED DUE TO LACK OF A SECOND.

MR. GREEAR MOVED THE DRUGS IN THIS CLASS WERE THERAPEUTIC ALTERNATIVES. SECONDED BY DR. BRIGGS. THE MOTION PASSED WITH ONE OPPOSED.

15. Re-review of Urinary Antispasmodics (Red Category)

HEATHER MORROW: A representative of Allergan discussed Sanctura XR. Although anti-muscarinics are first line therapy for over active bladder, the clinical usefulness of this class has been limited by dose dependant adverse events. As the only once daily product, there are three important areas where Sanctura XR's unique properties can provide potential benefits when compared to the other anti-muscarinic agents, which were reviewed. We request that Sanctura XR be added to the PDL.

TONI SHULL: A representative of Astellas discussed VESIcare. Efficacy data from four new trials were reviewed. VESIcare should be retained on the PDL for the following reasons. It restored continence in over 50 percent of patients that were incontinent during short-term and long-term treatment. Across multiple trials, VESIcare demonstrated statistically significant reductions in urgency and urgent continence. It also demonstrated a statistically significant increase in warning time.

DAVID GROSS: A representative of Pfizer discussed Toviaz (Fesoterodine). Fesoterodine is a new anti-muscarinic agent for the treatment of OAB. It was approved by the FDA in October of last year, but was not on the market at the last review. It has been approved for the treatment of overactive

bladder and associated symptoms of urinary incontinence, frequency, and urgency. It is available in two dosages, 4 and 8 milligrams. It is a pro-drug that is totally and rapidly hydrolyzed, which allow for more consistent and predictable levels. Two trials focusing on the efficacy and safety of both dosage forms of Toviaz were reviewed. As with other drugs in this class, the most common adverse events were dry mouth and constipation. However, discontinuation due to the most common adverse event, dry mouth, was low at less than 1 percent with the 8-milligram dose. Toviaz is the first anti-muscarinic drug to launch with safety data from a three-year open label extension study within its label, which was reviewed. Toviaz can be taken anytime during the day without regard to food. Doses greater than 4 milligrams are not recommended in patients with severe renal insufficiency. Toviaz also comes with a comprehensive patient support plan called Your Way, which was designed to educate and empower patients to help manage their OAB symptoms and set realistic expectations about treatment. Your Way was further reviewed.

Dr. Sater gave the First Health presentation on Urinary Antispasmodics. There are six available entities in this class with 11 products, both branded and generic. There is one transdermal product and one topical gel. There is similar efficacy across the class. The adverse drug reaction profiles differ. Better patient tolerability is found with the newer agents and dosage forms versus the old Oxybutynin immediate release. In October, there were 373 claims: 50% for Detrol LA, 13% for VESIcare, 12.5% for Enablex, 7.25% for extended release Oxybutynin, 6% for immediate release Oxybutynin, and less than 10% for the rest. At the last review and without discussion, the motion for a class effect, to include at least one long-acting entity, passed unanimously. Since the last review, Toviaz was added to the marketplace. Dr. Kevin Tamara prefers Toviaz to others in this class. He feels it has superior efficacy and tolerability. Dr. Paul Furuchi has had success with Toviaz in his refractory patients and feels it is well tolerated.

In response to Dr. Demain, Dr. Sater said the currently preferred drugs were Detrol LA, VESIcare, Enablex, immediate release Oxybutynin, and Oxybutynin syrup.

DR. DEMAIN MOVED A CLASS EFFECT WITH ONE LONG-ACTING AGENT TO BE INCLUDED ON THE PDL. SECONDED BY DR. BRIGGS. THE MOTION PASSED UNANIMOUSLY.

16. Re-review of Antidepressants SSRIs (Blue Category)

There were no public testimonies.

Dr. Sater gave the First Health presentation on Antidepressants SSRIs. There are six available entities, both immediate and extended release preparations in varying dosage packages. There is one combination. Minute affinities for other receptors vary between the agents and may account for subtle differences in the adverse drug reaction profiles. The efficacy is similar among all agents. In October, there were 2,990 claims: 12 claims for liquid, 26% for Sertraline, 25% for Fluoxetine, 20% for Lexapro, 14% for Escitalopram, 10% for Paroxetine, and less than 6% for the rest. At the last review, there was no discussion. The motion to include at least three SSRIs including either Citalopram, Escitalopram, or Sertraline, and preferentially including Fluoxetine solution, passed with three opposed.

DR. PHILLIPS MOVES TO INCLUDE AT LEAST THREE SSRIs INCLUDING EITHER CITALOPRAM, ESCITALOPRAM OR SERTRALINE, AND PREFERENTIALLY INCLUDING FLUOXETINE SOLUTION ON THE PDL. SECONDED BY DR. LILJEGREN.

The committee discussed whether the motion had to be so complicated. It was noted that every drug, except for Lexapro, was now available as a generic.

THE MOTION FAILED WITH ALL OPPOSED.

DR. PHILLIPS MOVED A CLASS EFFECT, TO INCLUDE AN ORAL SOLUTION. SECONDED BY DR. MICHAUD.

Dr. Liljegren noted that Citalopram had been included on the PDL, because it was indicated for pregnant patients.

THE MOTION PASSED WITH ONE OPPOSED.

17. Re-review of Androgenic Agents (Green Category)

Dr. Sater gave the First Health presentation on Androgenic Agents. There is one chemical entity, Testosterone, in this class. There are three available products: two topical gels and one transdermal product. All are effective for the treatment of primary and secondary hypogonadism. Adverse drug reaction profiles are similar with the transdermal system causing more local irritation, secondary to adhesive. In October, there were 14 claims: 12 for Androderm, and 1 claim each for Testim and Androgel. The preferred agents are Androderm and Androgel. At the last review and without discussion, a motion for class effect passed unanimously.

DR. BRIGGS MOVED A CLASS EFFECT. SECONDED BY MS. STABLES. THE MOTION PASSED UNANIMOUSLY.

18. Re-review of COX II Inhibitors (Green Category)

Dr. Sater gave the First Health presentation on COX II Inhibitors. There are two agents for consideration, Celebrex and Meloxicam. Meloxicam is COX II specific at lower doses, but non-specific at higher doses. Indications are varied. The efficacy and adverse drug reaction profiles are similar. In October, there were 266 claims: 65.5% for Celebrex and 35% for Meloxicam. Both of the agents are currently preferred. At the last review and without discussion, a motion for class effect passed with one opposed.

DR. BERGESON MOVED A CLASS EFFECT. SECONDED BY MR. GREEAR. THE MOTION PASSED UNANIMOUSLY.

19. Re-review of Anticonvulsants 1st Generation (Green Category)

Dr. Sater gave the First Health presentation on Anticonvulsants 1st Generation. This widely varied class includes a wide variety of chemical entities and mechanisms. The preferred agents in the Carbamazepine Derivatives are Oxcarbazepine, Carbamazepine, Tegretol XL, Carbatrol,

Carbamazepine, Trileptal suspension, and Epitol. In October, there were 1,713 claims for drugs in the Carbamazepine and 1st Generation anticonvulsants: 45% for Oxcarbazepine tablets, 15% for Carbamazepine tablets. Moving to the other path of the anticonvulsants, 27% for Divalproex, 23% for generic Depakote, 15% for generic Dilantin, 8.5% for Dilantin branded, 5% for generic Depakote sprinkles, and less than 12% for the rest. At the last review and without discussion, a motion stating all drugs were therapeutic alternatives and at least one agent from each chemical entity be included on the PDL failed. After a brief discussion, a motion stating all agents are therapeutic alternatives and to accept the bids passed with four opposed.

DR. BERGESON MOVED THE DRUGS IN THE CLASS WERE THERAPEUTIC ALTERNATIVES. SECONDED BY DR. KILEY.

It was noted that with the motion, one drug from each class would not necessarily be included on the PDL. Mr. Campana noted that this class had many generics so there would be a wide representation with just the generics available.

THE MOTION PASSED WITH TWO OPPOSED.

20. Re-review of Growth Hormones (Green Category)

Dr. Sater gave the First Health presentation on Growth Hormones. All products in this class are recombinant growth human growth hormones or Somatropin. The indications and delivery devices vary widely. The currently preferred agents are Nutropin, Genotropin, Norditropin, and Nutropin AQ. In October, there were 23 claims: 48% for Nutropin AQ, 26% for Genotropin, 8.7% for Norditropin, 8.7% for Nutropin, and 4.35% for Humatrope (the only non-preferred agent), and 4.35% for Nutropin AQ. At the last review and without discussion, the motion for a class effect passed unanimously.

In response to Dr. Liljegren, Dr. Sater said there were no comments from pediatricians or pediatric endocrinologists. It was noted that there were no pediatric endocrinologists in the State of Alaska.

DR. BERGESON MOVED A CLASS EFFECT. SECONDED BY DR. DEMAIN. THE MOTION PASSED UNANIMOUSLY.

21. Re-review of H2RA (Green Category)

Dr. Sater gave the First Health presentation on Histamine2-Receptor Antagonists. There are four available agents and all are available as generics. They have similar indications and efficacy. The drug interaction profile for Cimetidine is more concerning than the others. The currently preferred agents are Ranitidine, Ranitidine syrup, and Famotidine. In October, there were 840 claims: 70.36% for Ranitidine, 16% for Famotidine, and 10% for Ranitidine syrup. At the last review and without discussion, the motion for a class effect to include a suspension and tablet formulation, and exclude Cimetidine, passed unanimously.

DR. LILJEGREN MOVED A CLASS EFFECT, INCLUDING ONE PEDIATRIC PREPARATION AND EXCLUDING CIMETIDINE. SECONDED BY DR. DEMAIN. THE MOTION PASSED WITH ONE OPPOSED.

22. Review Minutes from September 2009 Meeting

Mr. Campana reviewed the corrections to be made to the September 2009 meeting minutes.

DR. KILEY MOVED TO APPROVE THE SEPTEMBER 2009 MEETING MINUTES AS CORRECTED. SECONDED BY DR. DEMAIN. THE MOTION PASSED UNANIMOUSLY.

23. Comments from Committee Members or Chair

Dr. Brodsky thanked Dr. Sater for her contributions to the P&T Committee over the years. Dr. Sater expressed her appreciation in working with the Alaska P&T Committee. She will be working with Idaho in the future.

Mr. Campana thanked everyone for their hard work in achieving the objective of providing the most vulnerable patients in Alaska with the best and most cost effective medications available. The two new members of the P&T Committee were welcomed. The agenda for the next meeting, January 22, 2010, was reviewed. Dr. Sater will be missed, but hopefully we will get a good replacement in the near future. We appreciate all the hard work she that has done for the committee.

24. Adjourn

The meeting adjourned at 11:37 a.m.